MEMORANDUM

DATE: January 10, 2005

SUBJECT: Glutaraldehyde: Submission of published articles under FIFRA 6(a)(2).

EPA Identification Numbers:

P.C. Code: 043901 MRID numbers: 45814601 through 45814607

TO: Dennis Edwards, Chief
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THRU: Norm Cook, Chief
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Action Requested: Review of information submitted in published articles on hazards of glutaraldehyde under FIFRA 6(a)(2). Determine if expedited review or label changes are necessary.

Background

Union Carbide Corporation, a subsidiary of Dow Chemical Corporation, submitted seven published articles on gluteraldehyde. The submitted articles are as follows:

1) MRID 45814601: Resrat, A., Polan, C., Henderson, L.M. (1969): Mammalian Metabolism of Glutaric Acid. Journal of Biological Chemistry 244(6): 1461-1467.

2) MRID 45814602: Packer, L and Greville, G.D. (1969): Energy-linked Oxidation of Glutaraldehyde by Rat Liver Mitochondria. FEBS Letters 3(2): 112-114.

3) MRID 45814603: Myers, D.R. et al (1986): Systemic Absorption of 14-C Glutaraldehyde from Glutaraldehyde-treated Pulpotomy sites. Pediatric Dentistry 8(2): 134-138.

4) Karp, W.B., Korb, P., Pashley, D. (1987): The Oxidation of Glutaraldehyde by Rat Tissues. Pediatric Dentistry 9(4): 301-303.

5) MRID 45814605: Ranly, D.M., Amstutz, L., Horn, D. (1990): Subcellular localization of Glutaraldehyde. Endod. Dent. Traumatol. 6: 251-254.

6) MRID 45814606: Vergnes, J.S. and Ballantyne, B (2002): Genetic Toxicology Studies with Glutaraldehyde. Journal of Applied Toxicology 22: 45-60.

7) MRID 45814607: Van Miller, J.P. et al. (2002): Chronic Toxicity and Oncogenicity Studies with Glutaraldehyde dosed in the Drinking Water of Fischer 344 Rats. Toxicology 175: 177-189.

Summary of Information in the submitted published papers

1) The submitted paper MRID 45814601, reports on the metabolism of glutarate (glutaric acid) in rat liver mitochondria "with emphasis on the enzyme system which catalyzes dehydrogenation and subsequent decarboxylation of glutaryl-CoA." Glutaric acid is not the same chemical as glutaraldehyde. A previous submission to the Office of Pesticide Programs on the metabolism and toxicity of glutaraldehyde metabolites (MRID 45779401) suggested that glutaraldehyde would be oxidized to glutaric acid by aldehyde dehydrogenase, followed by conjugation with S-adenosyl CoA and then catabolism to acetoacetate and carbon dioxide. However, there is little data on toxicity of glutaraldehyde metabolites. Studies of glutaric acid in the open literature show no evidence of teratogenicity or mutagenicity but no data on glutaric acid have been formally reviewed by the Office of Pesticide Programs. A more detailed study of glutaric acid would be needed should it be necessary to to so.

2) The submitted paper, MRID 45814602, reports on biochemical reactions of glutaraldehyde in rat liver mitochondria. This paper shows that rat liver mitochondria have the ability to rapidly oxidize glutaraldehyde and is strictly a biochemistry oriented type of publication with no apparent toxicological implications at this time.

3) The submitted paper, MRID 45814603, reports on the systemic absorption of radiolabelled glutaraldehyde using the dog as experimental animal. Pulpotomies were performed on 5 mongrel dogs, after which a cotton pellet containing radiolabelled glutaraldehyde was placed on each pulpotomy site for 5 minutes. Whole blood, urine, and expired air were collected up to 90 minutes post-dose at which time the animals were sacrificed and tissue levels of radioactivity measured. Absorption of glutaraldehyde was demonstrated from the pulpotomy sites in this study, and tissue levels were low, with the remaining glutaraldehyde excreted in urine. It is not surprising that glutaraldehyde would be absorbed from the oral cavity. However, it was noted in the paper that gradual impariment of the microcirculation of the pulp occurred following glutaraldehyde application.

4) The submitted paper, MRID 45814604 reports on metabolism of radiolabelled glutaraldehyde in tissue slices prepared from rat liver, heart, kidney, and muscle. As measured by radiolabelled CO2 production, the rank order of metabolism activity was liver>heart>muscle>kidney using tissue slices. Metabolism was also demonstrated in kidney mitochondrial fraction. This paper did not report any specific metabolites but only assessed oxidation using CO2 release as an indicator.

5) The submitted paper, MRID 45814605, reports on subcellular localization of glutaraldehyde following intravenous administration of radiolabelled gluraraldehyde to two groups of 4 SD rats. Rats were sacrified 5 minutes or 1 hour after administration of the test chemical and localization of radiolabel was examined in cytosol, membrane, and nuclear fractions of the liver. The results indicated that radioactivity was significant in the cytosol and membrane fractions of liver cells but not in the nuclear fraction. The implication of this experiment is that glutaraldehyde has little potential for mutagenic activity in treatment of tooth pulp as it does not appear to reach the nucleus. This conclusion is tenuous at best, as the actual tissue of interest was not tested.

6) The submitted paper, MRID 45814606, reports on in vivo and in vitro mutagenicity experiments with glutaraldehyde. It should be noted that the Agency also possesses several studies on mutagenicity of glutaraldehyde in its database. In the Salmonella reverse mutation assay, glutaraldehyde was found to be non-mutagenic in strains TA98, TA1535, TA1537, and TA1538. A weak mutagenic response (2.3-fold increase in the first assay, 1.9-fold increase in the confirmatory assay) was observed for strain TA100. In an in vitro forward gene mutation assay using CHO cells, there was no clear increases in mutation frequency of the HGPRT locus in CHO cells in the presence or absence of S9 activation. In an in vitro sister chromatid exchange

assay, glutaraldehyde did not cause biologically significant increases in frequency of SCE per cell or SCE per chromosome. In a mouse micronucleus test, glutaraldehyde did not cause an increase in micronucleus formation in peripheral blood cells. However, there was no evidence of toxicity to the target cells as measured by decreased PCE:NCE ratio. In a rat bone marrow cytogenetics assay, there was no evidence of an increase in chromosomal aberrations.
The results reported in this paper are the same results listed in the one-liner database for glutaraldehyde (MRIDs 43010201, 43211601, 43213401, 42707301, and 42851701). It is curious as to why results are reported under FIFRA 6(a)(2) for mutagenicity that have already been reviewed by the Office of Pesticide Programs. The results reported in the paper are likely the published versions of the studies listed in the one-liner database.

7) The submitted paper, MRID 45814607, reports on the chronic toxicity and carcinogenicity of glutaraldehyde administered in the drinking water to male and female F344 rats for 104 weeks. The results of this paper are similar to results reported in the one-liner database under MRID 43191101. An assessment of the carcinogenicity potential of glutaraldehyde will be made by the Office of Pesticide Programs' Carcinogenicity Assessment Review Committee as part of the process of the Reregistration Eligibility Decision for glutaraldehyde.

Conclusions/Recommendations

The Antimicrobials Division, has examined the submitted articles. None of the currently submitted articles contain information that would warrant an immediate change in labeling.

Previous reviews by the Risk Assessment and Science Support Branch (RASSB) and EPA's Health Effects Division on the health effects of glutaraldehyde have indicated that glutaraldehyde is a potential respiratory and skin sensitizer as well as a dermal and gastric irritant (MRID #'s 43330201, 44631801, 00117061, 41089601, 41773601). Published scientific literature also indicates that health care workers are more than 8 times more likely to be allergic to glutaraldehyde than non-health care working peers (Contact Dermatitis, Vol. 43: 151-156, 2000). As has been recommended in a previous memorandum (D270999), the Risk Assessment and Science Support Branch recommends that label language be added to the Ucaricide® 250 label to reflect the sensitization potential of glutaraldehyde to the skin and respiratory tract. Other than this previous recommendation, the submitted data do not warrant any immediate change in labeling for glutaraldehyde products.